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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,025	03/31/2004	James Rasmussen	GC22.4-CON2	4968

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/814,025	Applicant(s) RASMUSSEN ET AL.	
	Examiner Daniel M. Sullivan	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *60-62*.
   Claim(s) withdrawn from consideration: *48-59,63-72*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Daniel M Sullivan, Ph.D.
Primary Examiner
Art Unit: 1636

Continuation of 3. NOTE:

First, Applicant has amended the Application Data Sheet such that the priority date, which was previously 23 December 1988, is now 22 December 1989, which amendment necessitates a new search to determine if the claims are free of the intervening art. Second, Applicant has amended the claims such that the number of exposed mannose residues comprised by the claimed glucocerebrosidase is defined by a comparison with "glucocerebrosidase recovered from untreated cells" rather than human placental glucocerebrosidase. The amendment substantially changes the scope of the claimed invention by changing the benchmark against which the metes and bounds of the claimed product are defined. Entry of the amendment would therefore require a new search and consideration of issues with respect to 35 USC §112. In particular, there is nothing in the claim to indicate that the "untreated cells" are of the same type as the treated cells with the exception of the treatment. The claims merely recite, "recovered from untreated cells." There is no definite article or adjective "said" to specify that the untreated cells are the same as the culture of mammalian cells capable of expressing human glucocerebrosidase of part (a) and the untreated cells are not even limited to being mammalian cells. Therefore, the claims might embrace a glucocerebrosidase produced from a culture of mammalian cells having a higher number of exposed mannose residues than does a human glucocerebrosidase recovered from untreated bacterial or yeast cells. In view of this alteration in scope, entry of the amendment would raise new issues requiring additional consideration and search.

Continuation of 11. does NOT place the application in condition for allowance because:

Claim Rejections - 35 USC § 112

Claims 60-62 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

With respect to the scope of the "human glucocerebrosidase" of the claims, Applicant argues persuasively that the amino acid sequence of a single human glucocerebrosidase polypeptide was known in the art at the time of filing and the "human glucocerebrosidase" of the disclosure refers to the known polypeptide.

However, Applicant's assertion that the skilled artisan would recognize Applicant was in possession of a genus of any human glucocerebrosidase produced by any mammalian cell treated with any inhibitor of carbohydrate processing that acts to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species, wherein said glucocerebrosidase is suitable for the treatment of a human patient having Gaucher's disease is not persuasive.

In response to the *prima facie* case and arguments of record, Applicant contends that the specification clearly contains written description for the term "mammalian cells". Applicant cites *Amgen v. Hoechst* 65 USPQ2d 1385 (Fed. Cir. 2003) and contends that, in the instant case as in *Amgen*, the term "mammalian cells" is used in the claims merely to identify the types of cells that may be utilized to make the claimed glucocerebrosidase pharmaceutical compositions.

This argument has been fully considered but is not deemed persuasive. As stated in the previous Office Action (p. 4, emphasis added):

> [T]he specification also teaches that, to be therapeutically useful as recited in the claims, the glucocerebrosidase must be post-translationally modified to provide a carbohydrate structure which will target to human mannose receptors (see especially the paragraph bridging page 26-27). The specification further teaches that such a glucocerebrosidase has at least two carbohydrate moieties each having a Man_3-Man_9 structure and such rGCR represents at least 50% of the rGCR provided in the therapeutic composition (page 27, lines 1-4). However, the specification provides no specific disclosure of which

combination within the broad scope of a glucocerebrosidase produced by any mammalian cell exposed to any inhibitor of carbohydrate processing that acts to inhibit conversion of $Glc_3Man_9GlcNac_2$ to smaller species will comprise the requisite carbohydrate structure.

Thus, the rejection does not assert that the genus "mammalian cell" has not been described, but that the combination of mammalian cell and inhibitor of carbohydrate processing required to produce a glucocerebrosidase having at least two carbohydrate moieties each having a Man3-Man9 structure wherein such rGCR represents at least 50% of the rGCR has not been described. In contrast to the facts in *Amgen*, wherein many thousands of species of "mammalian cell" were known in the art at the time of filing, combinations of mammalian cells and inhibitors of carbohydrate processing capable of producing a human glucocerebrosidase having the carbohydrate properties of a therapeutically useful glucocerebrosidase described in the specification were not conventional in the art the time of filing.

Finally, Applicant contends that the showings of the Declaration under 37 C.F.R. §1.132 provided after final rejection establishes that human glucocerebrosidase produced in three different mammalian cell lines treated with four different inhibitors of carbohydrate processing that act to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species contain a higher number of exposed mannose residues than glucocerebrosidase recovered from untreated cells.

As Applicant's response fails to provide good and sufficient reason as to why the evidence filed after final rejection was not earlier presented, the Declaration has not been entered. In particular it is noted that the final rejection did not include any grounds for rejection that might necessitate an evidence declaration that were not already presented in the prior non-final rejection. As the Declaration has not been entered, the particulars thereof will not be addressed in this Advisory Action. It is noted, however, that it is not clear from the data

presented that each of the enzyme preparations produced by the various cell lines in the presence of the various inhibitors have the properties of a pharmaceutically useful glucocerebrosidase as contemplated in the specification (i.e., having at least two carbohydrate moieties each having a Man_3-Man_9 structure and such rGCR represents at least 50% of the rGCR).

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Claims 60-62 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the claims are rejected because the specification, while being enabling for a pharmaceutical composition suitable for the treatment of a human patient having Gaucher's disease comprising a human glucocerebrosidase produced by providing a culture of CHO cells capable of expressing said human placental glucocerebrosidase and treating the CHO cells with deoxy-mannojirimycin, swainsonine, castanospermine, deoxy-nojirimycin or N-methyl-deoxynojirimycin, does not reasonably provide enablement for the broad scope of a pharmaceutical composition suitable for the treatment of a human patient having Gaucher's disease comprising a human glucocerebrosidase produced by providing a culture of any mammalian cell capable of expressing a human glucocerebrosidase and treating the cell with any inhibitor or carbohydrate processing that acts to inhibit conversion of $Glc_3Man_9GlcNac_2$ to smaller species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As discussed above, Applicant's contention that the "human glucocerebrosidase" of the disclosure refers to the polypeptide known in the art at the time of filing is persuasive.

Applicant's arguments with regard to predictability of glycosylation in cell culture are based on the showings of the Rule 1.132 Declaration, which for the reasons stated above will not be entered after final rejection. It is again noted that it is not clear from the data presented that each of the enzyme preparations produced by the various cell lines in the presence of the various inhibitors have the properties of a pharmaceutically useful glucocerebrosidase as contemplated in the specification (i.e., having at least two carbohydrate moieties each having a Man_3-Man_9 structure and such rGCR represents at least 50% of the rGCR).

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.